NIH POLICY MANUAL

54107 - REVIEW OF APPLICATIONS AND AWARD OF GRANTS INVOLVING HUMAN SUBJECTS

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1. **Explanation of Material Transmitted:** This chapter specifies the NIH policies and procedures for the protection of human subjects involved in NIH-supported extramural assistance awards, i.e., those funded by grants and cooperative agreements, hereinafter referred to as grants. It also serves to implement Part 46, Title 45, of the "Code of Federal Regulations" (45 CFR 46) as amended and Section 491, Title IV of the Public Health Service Act. This manual chapter is applicable to contracts where appropriate.

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A. Purpose:

This chapter states the NIH policies and procedures for the protection of human subjects involved in NIH-supported extramural assistance awards, i.e., those funded by grants and cooperative agreements, hereinafter referred to as grants. It also serves to implement Part 46, Title 45, of the Code of Federal Regulations (45 CFR 46) and Section 491 of the Public Health Service Act.

The policies and procedures set forth in this chapter supersede previous NIH instructions related to protection of human subjects under NIH grants. (The NIH policy for activities conducted under contracts is in NIH Manual Chapter 6000-3-4.55.)

B. Applicability:

Except for research which is exempt (see below) or waived by the Secretary, HHS, this policy is applicable to all NIH grant applications and awards in which human subjects (as defined below at E.2) are involved.

Exempt Research Categories (45 CFR Section 46.101(b))

Unless otherwise required by Department or Agency heads, research activities in which the only involvement of human subjects will be in one or more of the following categories are exempt from this policy:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior, unless: (i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation; and (iii) this exemption generally does not apply to research with children.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if: (i) The human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

4. Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

5. Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine: (i) Public benefit or service programs; (ii)

procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs and procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs.

6. Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

C. Background:

The National Advisory Health Council, after a study of the issues pertaining to clinical research and investigations involving human subjects, forwarded to the Surgeon General of the Public Health Service in December 1965 a recommendation which was incorporated into a policy issuance, dated February 8, 1966 (PPO #129). NIH, PHS, and Department policies have been formally evolving since then. Final regulations (45 CFR 46), upon which this chapter is based were most recently published on June 18, 1991, (56 FR 28003). Subpart A of the DHHS regulations now comprises The Common Federal Policy (Common Rule) for the Protection of Human Subjects, applicable to 16 Executive Departments/Agencies.

D. References:

1. Code of Federal Regulations, Title 45, Part 46, (see Appendix 1).
2. Public Health Service Act, Section 491, (42 U.S.C.2891-3).
3. DHHS Grants Administration Manual Chapter 1-40, Protection of Human Subjects.
4. PHS Grants Administration Manual Part 107, Protection of Human Subjects.
5. NIH Manual Chapter 6000-3-4.55, Contracts Involving Human Subjects.
6. NIH Manual Chapter 4104, NIH Research Grants to Foreign Institutions and International Organizations.
7. NIH Manual Chapter 4805, Research Grants Awarded to Non-Affiliated Individuals.
8. Code of Federal Regulations, Title 21, Subchapters D, F, and H; Food and Drug Administration.
9. Multiple Project Assurance List (M.P.A.L.) of institutions in general compliance with DHHS regulations. (Issued by the Office for Protection from Research Risks (OPRR), and available through a constantly updated listing at:

&CUN1DAJ.MPAFLIST.CURRENT ON CAT.)

E. Definitions:

1. Assurance - the documentation approved by the OPRR from a grantee or a prospective grantee, assuring institutional compliance with and implementation of regulations for the Protection of Human Subjects (45 CFR 46).

2. Certification - official notification by the institution to DHHS in accordance with the requirements of 45 CFR 46 that a research project or activity involving human subjects has been reviewed and approved by the Institutional Review Board (IRB) in accordance with an approved Assurance on file with OPRR that covers the research to be conducted. Certification is required when the research is supported by the Department and not otherwise exempt in accordance with 45 CFR Section 46.101(b).

3. Expedited Review - a review that may be performed in accordance with Section 46.110 by delegation from the IRB to the IRB chairperson or an experienced reviewer. Expedited review is appropriate only if the proposed research would involve no more than minimal risk and the human subjects involvement falls into one of the categories listed in page 17, Appendix 1. Minor changes in previously approved research may also be given expedited review during the period for which approval is authorized. In DHHS-approved research only Multiple Project Assurance (MPA) institutions may perform expedited review.

4. Human Subject - a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information. (For further clarification see 45 CFR Section 46.102, Appendix 1.)

5. Informed Consent - the process of obtaining legally effective informed consent of the human subject or the subject's legally authorized representative, to allow sufficient opportunity to consider whether to participate and to minimize the possibility of coercion or undue influence.

   The basic elements of information necessary to such consent are given at 45 CFR Section 46.116(a). Additional elements to be provided when appropriate are given at Section 46.116(b). Conditions permitting alteration or waiver of the requirements for informed consent are given at Section 46.116(c) and (d).

6. Institution - any public or private entity or agency (including Federal, State, and other agencies).

7. Institutional Review Board (IRB) - a board or committee charged with responsibility for review of research activities involving human subjects conducted at or sponsored by the institution. The composition of the IRB and details of its procedures and responsibilities are specified at 45 CFR Sections 46.107, 46.108, 46.109, 46.110, and 46.111 and included in the Institutional

Assurances as approved by OPRR.

8. Legally Authorized Representative - an individual or judicial or other body authorized under applicable law to give permission on behalf of a prospective subject to the subject's participation in the research.

9. Minimal Risk - means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

10. Multiple Project Assurance List (M.P.A.L.) - a list of institutions having DHHS-approved assurances with general applicability. Issued by OPRR and available through a constantly updated listing at:

    &CUN1DAJ.MPAFLIST.CURRENT ON CAT.

F. Policy:

NIH policy is that no research activity involving human subjects, unless specifically exempt under Section 46.101(b) or waived under Section 46.101 (i) shall be supported by NIH until the requirements of 45 CFR 46 and this manual chapter have been met. While the responsibility for the determination that all such requirements are met and that the rights and welfare of human subjects have been and will be adequately protected resides at all levels of institutional and NIH review, the final responsibility lies with the awarding ICD.

G. Implementation:

1. Institutional Responsibility

    a. General

    The grantee has primary responsibility for safeguarding the rights and welfare of human subjects in research conducted at or sponsored by the grantee. Grantee documentation of Assurances of Compliance with, and implementation of, the regulations for the Protection of Human Subjects (45 CFR 46), when approved by DHHS (OPRR), establish accountability for this responsibility.

    b. IRB Review of Research

    As provided in 45 CFR 46:

    (1) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove provisions for safeguarding the rights and well being of human subjects in all research activities covered by these regulations.

    (2) An IRB shall require that information given to subjects as part of the

process of obtaining informed consent is in accordance with Section 46.116. The IRB may require that information, in addition to that specifically mentioned in Section 46.116, be given to the subjects when in the IRB's jugment the information would meaningfully add to the protection of the rights and welfare of subjects.

(3) An IRB may permit alteration or may waive the requirements of informed consent in certain circumstances with appropriate documentation of IRB action in accordance with Section 46.116(c) or (d).

(4) The IRB may require, where appropriate, as in large scale clinical trial activities, that the research plan make adequate provision for monitoring the data collected to ensure the safety of subjects.

c. Certification

The certification of IRB review and approval is required for all research involving human subjects, except that which is exempt as given at 45 CFR Section 46.101(b). The date of approval must be within one year of the receipt deadline date for which the application is submitted. The IRB review should identify whether the proposed research qualifies for exemption status under a given category of Section 46.101(b).

When an exemption status is identified on the face page of the application, the above certification is not required. However, an adequate explanation should be provided in the application under the heading of Human Subjects to allow a determination that the designated exemption is appropriate.

When the grantee institution has an OPRR-approved MPA, it is preferable that this certification is submitted with the application. If not, it must be received within 60 days after the application deadline date or as otherwise prescribed by the Scientific Review Administrator (SRA), whichever comes first. It should be sent to the SRA, and not to OPRR.

This certification may be provided in any one of several ways. The applicant may provide it only on the face page of the application, use Optional Form 310 (formerly HHS 596), use an institutional format, or provide it on plain paper giving equivalent information.

An institution that already has an MPA must provide the Assurance number on the face page of the application. In addition, it should provide the above certification of initial IRB review, or of IRB continuing review for the non-competing application (for which there is no grace period) in the manner described above. In the absence of certification, the application will be considered incomplete and the SRA will defer its review to a later cycle.

An institution lacking a valid assurance, but involving human subjects in research, must declare its intention to comply with 45 CFR 46 as specified in the Application Kit. When an award is contemplated and OPRR is requested to negotiate a Single Project Assurance (SPA), certification will be included as part of the institution's assurance document submitted to OPRR.

2. NIH Responsibility

   In accordance with 45 CFR 46, DHHS will review all applications involving human subjects for compliance with the regulations. Review will be conducted by officers and employees of DHHS with responsibility for policy and program development and staff review of grant applications. Research grant applications involving human subjects will also be evaluated by such experts or consultants as the Secretary determines to be appropriate. The evaluation will consider the risks to subjects, the adequacy of the protection against the risks, potential benefits of the proposed research to the subjects and others, and the importance of the knowledge to be gained. At NIH this evaluation is normally accomplished in conjunction with peer review for technical and scientific merit by the IRGs, as well as reviews by the National Advisory Councils and Boards, staff of the NIH awarding unit and where appropriate, OPRR.

   In special instances when current or past evaluations suggest the need to review the informed consent form to be used in connection with a grant project, the pertinent review or program official may request that form. Subsequent evaluation of the document should become part of the documentation in the application or grant file. Informed consent forms submitted at the initiative of applicants may be subjected to NIH review.

3. Office for Protection from Research Risks (OPRR)

   OPRR has Department-wide authority and responsibility for implementing 45 CFR 46, including: interpretation of the regulations; negotiation of Assurances of Compliance, and other matters relating to the Assurances filed by grantee institutions; compliance oversight; and providing clarification and guidance with respect to ethical issues raised in connection with research involving human subjects. Specifically OPRR:

   a. Negotiates Assurances with institutions seeking grants in support of research involving human subjects.

   b. Assists and informs NIH review groups regarding their responsibilities concerning human subjects protection.

   c. Assists and advises NIH staff concerning involvement of human subjects in research activities.

   d. Investigates possible instances of noncompliance with DHHS or NIH policy.

e. Approves all forms, instructions and procedures concerning implementation of 45 CFR 46.

f. Periodically issues a Multiple Project Assurance List (M.P.A.L.) of institutions that have filed Assurances with general applicability. The list is also in the Information for Management, Planning, Analysis, and Coordination (IMPAC) system.

g. Arranges for referral of issues of general ethical concern for appropriate review.

h. Submits codes to the DRG to release bars-to-awards of grants when all human subjects concerns are satisfactorily resolved and appropriate notification from the ICDs has been received by the OPRR.

4. Institute, Center, and Division (ICD) Human Subjects Research Coordinator

   Each ICD Director is encouraged to designate a Human Subjects Research Coordinator, who may be the ICD representative serving as a member of the Extramural Programs Management Committee. The Coordinator will serve as the ICD resource to:

   a. Maintain liaison with OPRR.

   b. Provide information about the DHHS human subjects regulations.

   c. Assist and advise program staff on human subjects problems to present to the Council/Board.

   d. Serve as ICD consultant to determine course of action in dealing with procedures which give rise to ethical concerns with a view to averting possible hazardous consequences.

   e. Assure that ICD staff comply with NIH guidelines and procedures for protection of human subjects.

5. NIH Referral Office

   In the course of reviewing incoming applications prior to assignment to initial review groups and NIH awarding units, referral officers will make preliminary determinations regarding human subjects involvement using the codes listed below. Referral officers' determinations are independent of applicant institutions' indication of human subjects involvement.

   Code E1 - Human subjects involved - exemption category 1 designated.

Code E2* - Human subjects involved - exemption category 2 designated.

Code E3* - Human subjects involved - exemption category 3 designated.

Code E4* - Human subjects involved - exemption category 4 designated.

Code E5* - Human subjects involved - exemption category 5 designated.

Code E6* - Human subjects involved - exemption category 6 designated.

Code E7 - Human subjects involved - Multiple exemption categories designated.

Code E8 - Human subjects involved - Applicability of human subjects regulations waived by the Secretary, HHS.

Code 10 - No human subjects involved.

Code 20 - Human subjects involved and no appropriate exemption designated by the applicant institution.

Code 98 - Human subjects coding not applicable.

Code 99 - Human subjects code invalid, correction required.

6. NIH Initial Review

SRAs of all of NIH's initial review groups have the following specific responsibilities in the initial review of competing applications.

a. Assurances and Certifications

(1) During the administrative review of an application, the SRA will review it for involvement of human subjects even though the face or signature page may indicate no such involvement. Human subjects coding errors must be corrected prior to the IRG meeting.

The SRA may consult with OPRR whenever there is a question about the institutional review or about interpretation of applicable policies and regulations.

(2) The SRA shall determine the assurance status of the grantee institution, and; if it holds an MPA, whether valid certification of IRB approval accompanies the application or is pending. If certification has not been submitted or is not properly completed or validly dated, or an inappropriate exemption is cited, the principal investigator is to be notified by the IRG office, indicating the steps to be taken, the due date

(within 60 days after the application deadline date or as otherwise prescribed by the SRA, whichever is earlier), for providing proper certification (see G.1.c.) and the consequences of late submission. Applicant organizations not currently holding an MPA must only declare their intention to comply with 45 CFR 46 as specified in The Application Kit.

When exemption from the regulations is designated on the face or signature page of the application, the SRA will ascertain that the designation is appropriate. (See exemptions listed at B.)

(3) If a proper certification of IRB approval is not available from an MPA institution within the time specified above, the application shall be considered incomplete and deferred for the next review cycle. Institutional failure to submit certification will result in administrative withdrawal from further review and return of the application to the institution [see 45 CFR Section 46.103 (f)].

Applications Lacking Definite Plans for the Involvement of Human Subjects: (45 CFR Section 46.118) Certain types of applications for grants, cooperative agreements, or contracts are submitted to the Department with the knowledge that subjects may be involved within the period of funding but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants where selection of specific projects is the institution's responsibility; research training grants where the activities involving subjects remain to be selected; and projects in which human subjects' involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These projects need not be reviewed by an IRB before an award may be made. However, except for research described in 45 CFR Section 46.101(b) or (i), no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, as provided in these regulations, and certification submitted to the Department. Awards made under these conditions should contain a cautionary note to the applicant organization.

(4) When the application involves research categories that are restricted by Federal

NOTE: For information on how the SRA handles this situation, p. 15 paragraph C(2).

regulations, such as research involving pregnant women, human fetuses, human ova, prisoners, children, or other research for which 45 CFR 46

requires additional protections, the SRA shall review the application to determine whether the requirements of the appropriate subparts of 45 CFR 46 have been met. Detail is to be provided in the summary statement.

(5) Prior to the IRG meeting, and if the research is not exempted, the SRA shall note whether the applicant has addressed in the research plan under the heading "Human Subjects" all six items required and detailed in the instructions accompanying the Form PHS 398 application kit. (See Appendix 2.)

If this information has not been included, or is considered inadequate, the SRA shall request sufficient additional information so that the IRG may adequately evaluate protection for the subjects. If this material is not received by a date three weeks before the IRG meeting, the application shall be deferred.

b. Review by the Initial Review Group

The initial review is expected to reflect the collective standards of the professions represented within the IRG membership. In the review process, if human subject concerns are expressed by members, the SRA shall poll the IRG membership to determine if the area of concern represents a consensus. Provision shall be made for documentation of a minority opinion. Review criteria shall be applie uniformly, whether or not an institution has an approved Assurance and regardless of the applicant institution's state or country. In accordance with Section 46.120, review shall take into consideration the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the proposed research to the subjects and others, and the importance of the knowledge to be gained.

c. Recommendations of the Initial Review Group: For the proposed activity involving human subjects, the IRG may recommend:

(1) Approval of the activity without restrictions. (Code 30: Human subjects involved - grantee must have current MPA and IRB Certification on file - human subjects protections appear adequate.)

(2) Approval of the activity but IRG offers comment regarding human subjects protections. This comment must be transmitted to the institution and investigator by the awarding unit. (Code 32: Human subjects involved - grantee must have current MPA and IRB certification on file - human subjects protections appear adequate but IRG makes additional comment regarding human subjects protections. This comment must be in the form of a special "Human Subjects" note on the summary statement. Code 3 is also used for grants to MPA institutions that have one or more performance sites without an MPA,

and when an application lacks definite plans for the involvement of human subjects.)

(3) Limitations on the work proposed, the imposition of restrictions, need for the elimination of concerns relating to the protection of human subjects or for IRB review and approval of the application in light of an inappropriately claimed exemption. This recommendation, at the discretion of the IRG, need not delay the processing of the application, but proper IRB certification must be submitted and all concerns regarding human subjects must be resolved by the ICD with OPRR concurrence before an award is made. (Code 44: Human subjects involved - current MPA on file and IRB Certification received - human subjects protections appear inadequate - IRG documentation of limitations, restrictions, and concerns regarding human subjects protections required in the form of a special "Human Subjects" note on the summary statement.)

(4) Approval of the activity but no appropriate Assurance on file. (Code 45: Human subjects involved - Declaration submitted showing intent to file Assurance and to conduct IRB review - human subjects protections appear adequate.) This activity may not be funded until an appropriate Assurance is approved by OPRR, and certification of IRB review and approval is received.

(5) Approval of the activity but no appropriate Assurance on file and the IRG offer comment regarding human subjects protections. This comment must be transmitted to the institution/ investigator. (Code 47: Human subjects involved - Declaration submitted showing intent to file Assurance and to conduct IRB review - human subjects protections appear adequate but the IRG wishes to make additional comments regarding human subjects protections. This comment must be in the form of a special "Human Subjects" note on the summary statement.)

(6) Limitations on the work proposed, the imposition of restrictions, or the need for elimination of concerns relating to the protection of human subjects, when no Assurance is on file. This recommendation need not delay the processing of the application, but before an award is made, proper IRB certification must be submitted, all human subjects concerns must be resolved by the ICD, an appropriate Assurance must be approved by OPRR, and IRB review of the proposed activity must be completed. (Code 49: Human subjects involved - declaration submitted showing intent to file Assurance or conduct IRB review - however human subjects protections appear inadequate - IRG documentation of limitations, restrictions, and concerns regarding human subjects protections required in the form of a special "Human Subjects" note on the summary statement.)

(7) If the research risks are sufficiently serious and protection against the risks so inadequate as to make the entire application unacceptable. (Either Code 44 or 49, dependent on whether an MPA is on file: Human subjects involved - application not recommended for further consideration because of human subject concerns. The reasons for the no further consideration must be detailed in a special "Human Subjects" note on the summary statement.)

d. Preparation of Summary Statements and Coding Responsibilities

(1) The SRA shall review and correct any code designations reflecting human subjects involvement which were erroneously coded from the grant application at the time of receipt. Codes E1-8 (See Appendix 3) shall be used by the SRA to reflect human subjects involvement when a valid and belated claim of exemption is not on the grant application. Code 10, to reflect no human subjects involvement, is used when the application was miscoded as E1-8, or 20.

(2) Code translations as they are described in Appendix 3 will be printed by computer on all summary statements and on the IRG Resume of Pre-Council/Board reports. These translations will not diminish the responsibility of SRAs to detail in the "Human Subjects" note at the end of the summary statement, any restrictions, limitations, concerns and comments relating to the protection of human subjects.

(3) Following IRG review the SRA shall document that review by marking the IRG Data Sheet to reflect the recommendations of the IRG as described in section G.6.c. above. (Codes 30, 32, 44, 45, 47, and 49 are described also in Appendix 3.)

Codes 44, 45, 47, or 49 shall be assigned when it is determined that the protections for human subjects are inadequate, additional reviews are required and/or an Assurance must be negotiated. The assignment of Codes 44 through 49 will not necessarily delay the further processing of an application but will bar-the-award of funds for application until all concerns regarding human subject protections are satisfactorily resolved and any required Assurance and certification of IRB review is received and approved.

The SRA shall add a paragraph entitled "Human Subjects" at the end of the summary statement when Codes 32, 44, 47, or 49 are used. This paragraph shall detail al restrictions, limitations, concerns and comments relating to the protection of human subjects.

e. Distribution of Summary Statements

Summary statement, applications, and attendant documents shall not be sent to

OPRR by either DRG or the ICD SRAs unless they are coded 44 or 49. This procedure applies to application recommended for scoring and for those not recommended for further consideration.

7. Review by National Advisory Council or Board

   Only applications recommended for further consideration in which concerns regarding the involvement of human subjects were documented during the initial review shall be individually called to the attention of the appropriate National Advisory Council or Board. The Council or Board shall be asked specifically for concurrence or nonconcurrence with the IRG concern. Administrative matters need not be brought to Council's attention.

   Following Council or Board review, the NIH awarding unit shall record the Council or Board's specific comments and recommendations regarding these applications. Copies of all such Council or Board comments will not be sent by the ICD to the OPRR unless requested by OPRR. When requested, comments will be accompanied by appropriate notation of action taken or to be taken by the awardin unit, attaching copies of correspondence to the institution or indicating that the correspondence will follow.

8. Responsibilities of ICD Awarding Units

   a. Human Subjects Issues.

   (1) The program administrator shall review each application to determine prior to award of the grant that all human subjects issues and protections which appear inadequate as noted by the IRG or the Council/Board are satisfactorily resolved. Awarding unit staff may consult with the OPRR for advice.

   (2) Information regarding all restrictions, contingencies, or concerns regarding the involvement of human subjects shall be transmitted in writing by the program administrator to the official signing the application for the institution, with a copy to the principal investigator, whether the application is or is not recommended for further consideration, as soon as possible. A copy of all such documents must be sent to OPRR. If there are any questions, the program administrator should consult with the OPRR.

   (3) If the awarding unit deletes all or restricts any activities involving human subjects in connection with an award, the deletion or restriction must be specifically placed on th Notice of Grant Award (NGA).

   (4) A copy of each NGA and attachment restricting or prohibiting use of grant funds for research with human subjects is to be sent to OPRR.

   (5) As yet unresolved, human subjects issues may reach the NIH

awarding unit staff. No award can be made until such issues are resolved. Examples of issues include:

(a) Applications in which the IRG judges that protections appear to be inadequate. The specific limitations, restrictions or objections will be documented in the summary statement as required.

(b) Applications in which the Council or Board judges that protections, not identified by the IRG, appear to be inadequate and are so documented for the record.

(c) Applications that will require the completion and OPRR approval of an institutional Assurance.

(d) Applications in which the proposed research activity is restricted by sections of 45 CFR 46 and which require further examination and approval by the Secretary, HHS.

b. Human Subjects Codes.

All applications having unresolved human subjects issues should have been coded as 32, 44, 45, 47, or 49. Awarding unit staff should carefully check the Grants Management/ICMS work sheet to ensure that the correct human subjects code appears in the system. If the code is incorrect, staff shall request that OPRR make the necessary correction. When Codes 44, 45, 47, or 49 are assigned, the awarding of the grant is barred until identified concerns or conditions are satisfactorily resolved. Unless special arrangements are made with OPRR, documentation of the satisfactory resolution of human subjects concerns (i.e., Codes 44 and 49) must be transmitted to OPRR by program staff before grant management staff request OPRR to release the bar and permit the issuance of the NGA.

c. Institutional Assurance.

For each application recommended for further consideration which is likely to be funded and which requires negotiation of an Assurance (when the institution is not listed on the Multiple Project Assurance List), awarding staff should forward to the OPRR, as soon as possible, a request for negotiation of an Assurance. Attached to the request should be a copy of the application, summary statement, any relevant addenda, and information identifying the individual in the awarding unit who should be notified when the negotiation is completed and the Assurance is approved (see Appendix 4). Negotiations with a domestic institution usually require a minimum of three weeks. Ample time for negotiation should be allowed in advance of the proposed award date. OPRR will notify the awarding unit of the approval of a satisfactory Assurance and will submit a change of coding to DRG for release of the bar.

d. Cooperating Institutions.

When research will be conducted by cooperating awardee institutions, all awardee institutions not listed on the M.P.A.L., will require assurances before issuing an award.

e. Recertification.

When a year will have elapsed between the initial IRB review date certified by an institution holding an MPA and the anticipated award date, awarding unit staff shall require IRB re-review and certification prior to award.

9. Review and Award by NIH Awarding Unit of Noncompeting Applications

The awarding unit staff is responsible for reviewing noncompeting continuation applications, including those applications which reflect a change of grantee institution or principal investigator, for compliance with DHHS policy, as follows:

a. The program administrator shall determine whether human subjects are involved. When human subjects are involved, an IRB review, approval and annual recertification is required. In addition, the program administrator should be mindful that projects initially submitted with the intent of not involving human subjects, and hence not certified, may propose involving human subjects in a subsequent budget period. In this case, it is necessary for the awarding unit to require certification if the application is submitted by an institution with a valid Assurance, or to request OPRR to negotiate an Assurance and obtain a certification if the institution does not have an Assurance. If, upon review of an application, the program administrator, in consultation with members of the IRG and other qualified ICD staff, questions the acceptability of the risks or the adequacy of safeguards for subjects, approval for the involvement of human subjects may be withheld until such involvement is reviewed and recommended for approval by the IRG or Council/Board. A major modification of an application involving a change in research design to include human subjects requires the existence or establishment of an appropriate Assurance and review and approval by an IR and final approval by the program administrator and as appropriate, OPRR.

Applications Lacking Definite Plans for the Involvement of Human Subjects: (45 CFR Section 46.118) Certain types of applications for grants, cooperative agreements, or contracts are submitted with the knowledge that subjects may be involved within the support period, but definite plans would not normally be set forth in the application or proposal. These include activities such as institutional type grants when selection of specific projects is the institution's responsibility; research training grants in which the activities involving human subjects remain to be selected; and projects in which human subjects'

involvement will depend upon completion of instruments, prior animal studies, or purification of compounds. These projects need not be reviewed by an IRB before an award may be made. However, except for research exempted under Section 46.101(b) or (i) no human subjects may be involved in any project supported by these awards until the project has been reviewed and approved by the IRB, and certification submitted to the Department. The Optional Form 310 Form or institutional formatted letter may be used for its certifications. Institutional formatted letters must provide appropriate information.

b. If human subjects are involved, awarding unit staff will ascertain the presence and completeness of the IRB certification. Certification shall be within the 12 months preceding the requested award date.

c. No award may be made until a proper certification is received by NIH. If IRB certification has not been submitted with the application or is incomplete or is not validly dated, the awarding unit shall send a letter to the official signing for the institution and a copy to the principal investigator indicating what steps must be taken, the due date for the completed IRB certification (prior to budget period start date), and the possible consequences of a late submission. A lapse in support could occur if certification is delayed.

d. Awarding unit staff shall make any necessary changes in human subjects codes (Item 044) on the Grants Management/ICMS Worksheet to reflect the most recent status in human subject activity in the project, except that a change from Codes 44 through 49 will require OPRR action.

10. OPRR Coding Responsibility for Release of Bar-to-Award

    The following codes will be submitted to DRG by OPRR after receipt of a satisfactory solution of concerns (i.e., Codes 44 and 49) from program personnel and/or after an applicable Assurance has been approved by OPRR:

    Code 54 - Previously coded as 44 - All IRG, Council, and ICD concerns regarding human subjects protections have been resolved (awards).

    Code 55 - Previously coded as 45 - Assurance and certification of IRB review received and approved by OPRR.

    Code 57 - Previously coded 47. Assurance and certification of IRB review received and approved by OPRR.

    Code 59 - Previously coded 49. All IRG, Council, and ICD concerns regarding human subjects protections have been resolved (awards). Assurance and certification of IRB review received and approved by OPRR.

Refer to paper copy for Appendices 1 through 4

Last Updated: 07/20/00

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